Amendment to the Drawings

No changes to the drawings.

Remarks/Arguments

Claims 1-2, 7-25 are pending in this application. Claims 21-23 were withdrawn from consideration by the examiner. Claims 1, 14-20 have been amended. Claims 2, 7-13, 24-25 have been canceled. Claims 1, 14-20 were amended to more clearly claim what applicants consider to be their invention. Claim 26 has been added.

Continued Examination

The examiner withdrew the finality of the previous Office Action under 37 C.F.R. 1.114 based on the Request for Continued Examination filed 7-14-03. Examiner notes that Applicants' submission filed on [sic, Applicants note this submission was filed 4-15-03 under a Certificate of Mailing and received by the USPTO on 4-22-03] 4-22-03 was entered.

Election/Restrictions

The examiner made final the restriction requirement regarding claims 21-23 and considers the claims 21-23 withdrawn.

Claims 1, 2 and 7-20, 24-25 were examined by the examiner on the merits.

35 U.S.C. 102

Claims 16, 18, and 20 were rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/02002.

The examiner alleges that the claims are interpreted as drawn to a method of detecting cancer cells using antibody capable of binding to cancer marker for the purpose stated in the preamble of the claims, i.e., for determining status of a cancer, progression, and effectiveness of

an anti-therapy [sic]. WO 96/02002 is alleged by the examiner to teach detecting epithelial cancer cells using anti-E-cadherin and anti-alpha-catenin for determining status of a cancer, progression, and effectiveness of an anti-therapy. Note Examples at pages 30-49, Figs 1-3, claims 1-5, 7, and 8.

Response

WO 96/02002 discloses a method for determining relative invasiveness of an epithelial tumor which comprises determining a prognostic amount of a prognostic marker selected from the group consisting of E-cadherin and α-catenin in a cell sample and comparing the prognostic amount to a normal amount of the marker. Specimens were evaluated immunohistochemically for E-cadherin expression and correlated to histopathological grade, tumor stage, presence of metastases, and survival. The results indicated that E-cadherin expression could be used as a prognostic indicator for the potential of prostate cancer. Also demonstrated was a correlation between presence of expression of α-catenin in prostate tumor cells and survival.

The examples at pp 30-41 show correlation studies regarding E-cadherin. Tumor specimens were stained using either anti E-cadherin or HECD-1 MAbs. A correlation between degree of local extension of the tumor and aberrant expression of E-cadherin was found as well as the presence of metastases was significantly correlated with aberrant E-cadherin expression. The examples at pp. 41-48 show clinical evaluation of effects of decrease in E-catenin expression. Tumor specimens were stained with biotinylated anti-mouse Ig for E-cadherin and anti-rat Ig for α-catenin. Correlation was found between E-cadherin expression and tumor grade, tumor stage, survival or the advanced stage patients and progression free interval in patients with low stage disease. Also found was correlation between α-catenin and E-cadherin expression. The example 3 on p. 49 states that the results of the previous examples suggests use of the

markers in model systems to evaluate drug candidates for their ability to induce reexpression of the marker and thus dedifferentiation of tumors.

Figs 1-3 show 1) a photomicrograph of invasiveness of cells and corresponding labeling of the cells with an antibody to E-cadherin; 2) overall survival rate related to E-cadherin expression; and 3) progression free rate in patients after radical prostatectomy, respectively (i.e., data from Example 1).

Claims 1-5, 7, and 8 are drawn to a method for determining invasiveness potential of an epithelial tumor, which comprises determining a prognostic amount of a prognostic marker selected from the group consisting of E-cadherin and α-catenin in a cell sample obtained from a cell source containing cells of said tumor and comparing said prognostic amount to a normal amount of said prognostic marker in said cell source, wherein when said prognostic amount is less than said normal amount, said sample is indicative of invasiveness potential of said cells of said prostate tumor.

Therefore, Applicants respectfully traverse this rejection. Claims 16, 18, and 20 of the present invention, as previously presented or as presently amended, are not anticipated by the cited reference.

Claims 16, 18, and 20 have several limitations that are missing in the cited reference. The cited reference relates to evaluating a tumor for potential invasiveness based on presence of an aberrant amount of one of two markers or both markers in tumor cells. The tumor cells in the reference are already known to be epithelial tumor cells prior to testing for amount of or presence/absence of the marker(s).

Claim 16, as amended, is a method of determining the status of a cancer comprising:

a. obtaining a blood sample containing a cell from a patient diagnosed with cancer;

b. contacting the cell in the sample with a probe under conditions capable of forming a complex with an antigen of the cell;

c. detecting the complex, whereby detection of the complex can distinguish a non-cancer cell from a cancer cell;

d. determining the amount of cancer cells in the sample; and

e. correlating the amount of cancer cells in the sample with a stage of cancer, thereby determining the status of the cancer.

One limitation clearly missing from the reference is "whereby detection of the complex can distinguish a non-cancer cell from a cancer cell." The cited reference determines amount of marker which is correlated with invasiveness of the known cancer. The cited reference does not distinguish between cancer cells and non-cancer cells. Also missing is "determining the amount of cancer cells." The amount of cancer cells is pre-determined in the cited reference by choice of amount of tumor to be tested and the amount of the cells are not determined, rather the amount of marker is determined which does not necessarily correlate with amount of cancer cells. Since amount of cancer cells is not determined there can be no disclosure of a correlation step using the amount of cancer cells.

Claims 18 and 20, likewise, have these limitations or similar ones that are missing from the cited reference.

35 U.S.C. 103

Claims 1, 2, 7-15, 17, 19, 24, and 25 were rejected under 35 U.S.C. 103(a) as being unpatentable over either

U.S. Pat. 6,365,362 B1 (filing date Feb. 12, 1999) **or** Racila et al. for enriching step, **and** WO 97/38313 for detection step.

The claims are interpreted by the examiner as drawn to method of detecting circulating cancerous epithelial cells by enriching said epithelial cells first using something [that] binds to said epithelial cells, followed by detection of cancer cells using nucleic acid probes.

The examiner asserts that either U.S. Pat. 6,365,362 B1 or Racila et al. teaches how to enrich circulating epithelial [sic] steps using cytokeratin screening or magnetic particles connected to a ligand capable of binding epithelial cells. Note Method section of Racila et al. Also note Example 1 (column 17-22), claims 1, 2, and 6 of U.S. Pat. 6,365,362 B1.

WO 97/38313 is alleged by the examiner to teach all the reagents necessary to distinguish cancer cells from non-cancer cells using the hybridization pattern of nucleic acids (see page 21 to the first paragraph of page 26) and multiple probes (Example 7). The disclosed examples of probe associated with specific cancer and a genetic marker are PSMA, PSA, and centromeric regions of chromosomes 7, 8, 18 (page 21-22). Further, the examiner asserts that WO 97/38313 teaches method of determining status and progress of cancer patient, and monitoring efficacy of cancer treatment at page 3, lines 18-26, page 25, lines 19-26, examples 2, 7 and 11. Also note claims 1, 6, 7, and 15-17, 26, 29, and 31.

The examiner states that the combination of the three references fails to explicitly teach or suggest the claimed invention. However, various methods of distinguishing cancer cells from non-cancerous cells are known in the art to be used with combination of enriching circulating epithelial cells and the enriching the circulating cells using the method claimed in the instant invention is also known in the art. U.S. Pat. 6,365,362 teaches cancer metastasis involves shedding of epithelial cells in blood from the early stage of cancer development (State 1) but the detection is difficult to detect because the quantity is too small although detection of early shedding is critical for prevention [of] serious metastasis. See the background and Fig. 8. The

methods of the instant claims can be viewed as a method drawn to combining two steps known in the art, i.e., an In re Kerkhoven analysis (In re Kerkhoven, 626 F 2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)). The court held that it is obvious to combine two compositions, in order to form a third composition, when each of the two composition is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (MPEP 2144.06). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the enriching step and a detection step known to be useful for detecting shedding of epithelial cells by tumors with reasonable expectation of success.

Response

U.S. Pat. No. 6,365,362 B1 discloses an assay which combines immunomagnetic enrichment with multiparameter flow cytometric and immunocytochemical analysis to detect, enumerate and characterize carcinoma cells in the blood.

Racila is discussed in the present application on p. 28, line 29-p. 29, line 13. As pointed out on p. 29, lines 10-13 (emphasis added), "[t]his procedure has the capacity to detect whether epithelial cells are present in a sample, such as blood, but does not indicate the genetic status of the cells detected. Therefore further assays on the same sample are required to determine more conclusively the genetic status of these epithelial cells." The circulating epithelial cells were simply assumed to be tumor cells. (Applicants note that Jonathan Uhr is an author and contributor of the Racila *et al.* paper as well as an inventor of the present invention.)

Racila *et al.* (April 1998) disclose an assay combining immunomagnetic enrichment with multiparameter flow cytometric and immunocytochemical analysis to detect, enumerate, and characterize carcinoma cells in the blood. The cells were examined by flow cytometry for the presence of circulating epithelial cells. To determine whether the circulating epithelial cells were

neoplastic cells, cytospin preparations were made after immunomagnetic enrichment and were analyzed. The malignant nature of the cells was demonstrated by their cytology and immunophenotype. The assay consists of using a series of mAbs that recognize the tissue-specific molecules. The first step involves an immunomagnetic sample preparation. After separation, sample volume is reduced and enriched for epithelial cells (which is essential for obtaining the sensitivity and low background required). Then the elements in the cell suspension are tagged using a second mAb specific for cytokeratin, a third mAb against a pan leukocyte antigen (CD45), and a nucleic acid dye. The sample is then analyzed by flow cytometry, and all events staining with the nucleic acid dye are analyzed for CD45 and cytokeratin staining and light scatter characteristics. To examine whether the cells identified as epithelial cells by flow cytometry could be classified as tumor cells the cells were subjected to the immunomagnetic sample preparation followed by a cytospin that allows cells to be studied for morphology and additional markers. The total circulating epithelial cells measured by flow cytometry were used to assay for patients' clinical status over time. The goal of the assay was to perform screening entirely by immunomagnetic preparation followed by flow cytometry.

The antibodies CD45 and cytokeratin identify the cells as epithelial or non-epithelial based on the positive or negative staining of the cells viewed. This epithelial cell staining procedure confirmed that the epithelial cells were tumor cells by studying the morphology and markers of individual cells by use of cytospin.

WO 97/38313 discloses a method for enriching rare non-blood cells in a fluid sample comprising rare non-blood cells and non-rare cells, wherein the ratio of the rare non-blood cells to the non-rare cells is at least about 1:100,000, comprising obtaining a fluid sample, subjecting the fluid sample to density gradient separation and producing a first fluid comprising an increased concentration of rare non-blood cells and a second fluid comprising an increased concentration of rare non-blood cells, subjecting at least one of the fluids to a binding agent that

binds non-rare cells, and removing the bound non-rare cells from the fluid(s) to provide fluid(s) enriched with rare non-blood cells.

The method of the WO 97/38313 first runs a fluid sample (1) through density gradient separation. This gives a sample (2) with an increased concentration of rare non-blood cells (cancer cells/epithelial cancer cells). Sample (2) is then subjected to a "negative selection process". This entails subjecting sample (2) to an agent that binds the non-rare cells (blood cells) rather than the rare cells (cancer cells) ("positive selection process") ("precisely the opposite of conventional processes," p. 7, line 31). The bound non-rare cells are then separated from sample (2). Then the rare cells can be further processed, such as by identification, characterization and/or culturing. Embodiments of the methods are asserted to provide improved diagnosis, staging, and monitoring of cancer in a patient.

Claims 1, 14-15, 17, 19 as amended are not obvious in light of the Examiner's foregoing arguments nor do the conclusory statements about the general state of the art remedy the shortcomings of the arguments.

Claims 2, 7-13, 24-25 have been cancelled so any rejections to them are moot.

Conclusion

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

No fees are believed due. However, the Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Patricia L. Ades
Registration No. 44,496

NEEDLE & ROSENBERG, P.C.
Customer Number 23859
(678) 420-9300 Telephone
(678) 420-9301 Facsimile

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I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Patricia L. Ades — Date: Dec 17, 2003